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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/586,625	06/02/2000	Carlos F. Barbas III	22908-1227B	6568

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EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	PAPER NUMBER
1646	11

DATE MAILED: 02/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/586,625	Applicant(s) BARBAS ET AL.	
	Examiner Joseph F Murphy	Art Unit 1646	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the c rrespondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35,37-46 and 69-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35,37-46 and 69-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-35, 37-46, 69-73, drawn to SEQ ID NO: 1, with the elected species estrogen receptors, in Paper No. 10, 11/21/2001 is acknowledged.

Claims 1-35, 37-46, 69-73 are pending and under consideration.

Claim Objections

Claims 11 and 25 are objected to because of the following informalities: They contain subject matter drawn to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 13, 15, 16, 17, 18, 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

This is a genus claim. According to the specification (page 27, lines 1-13), the term variant means a protein which is mutagenized, truncated or has an insertion made to SEQ ID

NO: 1. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO: 1. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 1 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claims 9, 13, 15, 16, 17, 18, 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substantially purified polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 1, does not reasonably provide enablement for a protein variant of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 9, 13, 15, 16, 17, 18, 19 are overly broad in the recitation of "variant " since insufficient guidance is provided as to which of the myriad of polypeptide species encompassed by the claim will retain the characteristics of a zinc-finger nucleotide binding polypeptide. In the specification (page 27, lines 1-13), Applicants disclose that variants of the protein which is mutagenized, truncated or has an insertion made to SEQ ID NO: 1 without disclosing any actual or prophetic examples on expected performance parameters of any of the possible muteins of SEQ ID NO: 1. However, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another

in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is insufficient guidance provided in the specification as to how one of ordinary skill in the art would generate a zinc-finger binding protein other than those exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of claims 9, 13, 15, 16, 17, 18, 19 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 39-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering a composition comprising a fusion protein and a regulatable expression cassette that comprises at least one response element recognized by the nucleic acid binding domain of the fusion protein. See Eck & Wilson (Ref H of Paper No. 3) who report that numerous factors complicate *in vivo* gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See Eck and Wilson, page 82, column 1, first paragraph. These factors differ dramatically based on the protein being produced, and the disease and/or host being treated. It is further noted that Eck and Wilson supports the importance of tailoring a gene therapy vector and method to specific diseases and/or disorders and not to all diseases and disorders. See page 82, column 1, first paragraph. For example, Eck & Wilson et al. review the state of the art for gene therapy for inherited disorders and discloses that "[t]he level of protein function necessary to

achieve complementation of the defect varies widely among genetic diseases." See page 78, column 2, 2nd paragraph. As such, in light of the state of the art for gene therapy, the specification fail to provide guidance for any of the above parameters for *in vivo* gene expression nor do they provide a clear correlation to carrying out gene therapy with regard to any particular therapeutic effect with regard to any particular disease or disorder by administering the claimed composition.

To this regard, MPEP section 2164 sets forth that the issue of "correlation" is also dependent on the state of the art at the time of the invention. MPEP, section 2164 goes on to discuss that if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention broadly pertains, then there is lack of predictability in the art. Thus, what is known in the art provides evidence as to the question of predictability.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-35, 37-46, 69-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-5 are indefinite in the recitation of the term "derived from". It is unclear whether this term imposes a required limitation on the claim, such that it only encompasses, for example, polynucleotides amplified from human cDNA, or only sequences produced by

digestion with restriction enzymes of DNA isolated from human tissue that contains polynucleotides encoding the receptor, or if the claim encompasses all polynucleotide sequences that encode the receptor. Therefore, the metes and bounds of the claim are unclear.

Claims 4, 5 and 13 recite the term "selectivity", which is a conditional term and renders the claim indefinite. The metes and bounds of the claim thus cannot be ascertained. This rejection could be obviated by supplying specific parameters supported by the specification which Applicant considers to be "selective".

Claim 5 recites the term " Substantially ", which is a relative term and renders the claim indefinite. The metes and bounds of the claim thus cannot be ascertained. This rejection could be obviated by supplying specific parameters supported by the specification which Applicant considers to be " Substantially ".

Claims 1, 8, 69 recite the term "specifically", which is a relative term and renders the claim indefinite. The metes and bounds of the claim thus cannot be ascertained. This rejection could be obviated by supplying specific parameters supported by the specification which Applicant considers to be "specifically". Claims 2-7, 9-46, 70-73 are rejected insofar as they depend on the recitation of the term "specifically".

Claim 21 is vague and indefinite in the recitation of the terms "KRAB-ERD", "SID-ERD", "$(KRAB)_2$", etc. There is no definition within the claim to define the protein to which these acronyms refer. Thus, the metes and bounds of this claim cannot be determined

Claim 1, 8, 69 are rejected for recitation of the term "modular portion". There is no definition with which to determine what is a "modular portion" of the protein, thus the metes and

bounds of the claim cannot be determined. Claims 2-7, 9-46, 70-73 are rejected insofar as they depend on the recitation of the term "modular portion".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-19, 23-24, 26-31, 69-73 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent no. 5,217,867 (Evans et al.).

Evans et al. discloses receptor polypeptides, wherein the transcription trans-activation domains have been augmented in effect so as to produce novel entities that exhibit increased transcription initiation activity superior to the parent molecule (Column 1, lines 40-46). These receptor polypeptides comprise domains from members of the steroid hormone superfamily of receptors, including steroid receptor polypeptides, thyroid polypeptides, and retinoid polypeptides, including those of the human species (column 1, lines 30-40). Evans et al. discloses fusion polypeptides comprising a zinc-finger domain from the thyroid hormone receptor with the transactivation domain of the glucocorticoid receptor (column 5, line 63 to column 6, line 7; also see Figure 3), thus claims 1 and 2 are anticipated. This is a nuclear receptor, thus claim 3 is anticipated. This fusion protein has been altered such that its ligand selectivity is altered, thus claims 4 and 5 are anticipated. It is an inherent property of zinc-finger proteins to bind to a (GNN)n sequence, thus claims 6-7 are anticipated. The zinc finger domain could be considered a "variant" of a C2H2 modular unit, thus claims 8-10, 14-19 are anticipated.

Evans discloses that chimeric HGR-ER nuclear receptors have been constructed, thus claims 11-13 are anticipated. Evans et al. discloses the nucleic acid encoding the fusion proteins, host cells and vectors (Column 16, lines 5-60) thus claims 23-24, 26-31 are anticipated. Since the binding of nuclear receptors to DNA is an inherent property, and Evans et al. discloses the transfection of host cells by plasmids expressing the chimeric receptors, claims 69-73 are anticipated.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
February 7, 2002

DAVID S. ROMEO
PRIMARY EXAMINER